Neurophysiologic Aspects of Drug Abuse

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FP/Psych PGY-4

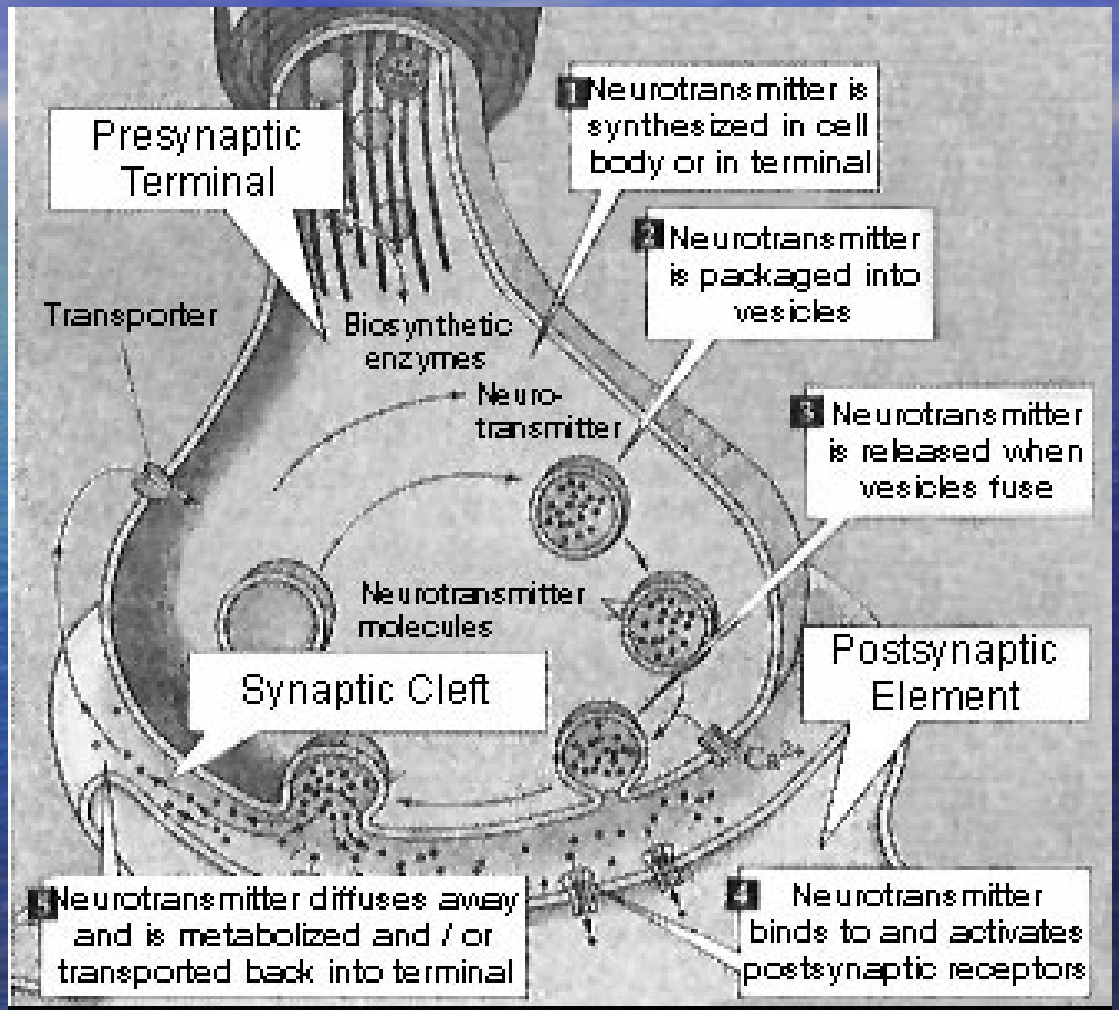
Outline

- Neurotransmitter Review
- Cocaine
- Amphetamine
- Opioids
- Phencyclidine
- Ketamine
- Marijuana
- Nicotine

Neurotransmitters

- Synthesized in Neuron
- Physiology Review
- Three types
  - Amino acids
    - Glutamate, aspartate, glycine, GABA
  - Monoamine
    - ACH, Dopamine, Epinephrine, Norepinephrine, Serotonin
  - Neuropeptides
    - Opioids, Substance P

Synpatic Cleft


Presynaptic Terminal
1 Neurotransmitter is synthesized in cell body or in terminal
2 Neurotransmitter is packaged into vesicles
Transporter
Biosynthetic enzymes
Neuro-transmitter
3 Neurotransmitter is released when vesicles fuse
Neurotransmitter molecules
Synaptic Cleft
Postsynaptic Element
5 Neurotransmitter diffuses away and is metabolized and / or transported back into terminal
4 Neurotransmitter binds to and activates postsynaptic receptors
Components of a Synapse

Dopamine

- Suppresses spontaneous activity of cortical neurons
- Plays an important role in reward mechanisms
- Four major dopamine systems
  - Mesolimbic
  - Mesocortical
  - Nigrostriatal – motor activity of basal ganglia
  - Tubuloinfundibular – regulates prolactin

Norepinephrine

- Produced locus ceruleus of brainstem
- Excitatory
  - Increase signal to noise ratio
- Associated with arousal, vigilance, and reward dependency
- Hyperactivity results in HTN, tachycardia, increased anxiety
- Low levels associated with depression

Serotonin

- Synthesized from Tryptophan in the Raphe Nucleus
- Modulatory Neurotransmitter
- Receptor decline in elderly may lead to depression
- Low Levels
  - Alcoholism, social isolation, impaired social function, binge eating
- High Levels
  - Harm avoidance, anorexia nervosa, compulsive behavior

Question

Which of the following factors differentiates substance dependence from substance abuse:

a. Chronicity of use

b. Interpersonal problems

c. Tolerance and withdrawal

d. History of successful rehabilitation

e. Failure to fulfill major obligations at work, home,

or school.

C

Cocaine

- Pharmacology
  - CNS Stimulants
  - Block reuptake of neurotransmitters
    - Dopamine
    - Norepinephrine
    - Serotonin
  - Causes presynaptic dopamine release
  - Blocks peripheral nerve impulses (local anesthesia)

Cocaine

- How is it ingested?
  - Injection, rare
  - Smoking the solid alkaloid form (crack)
  - Inhaled through the nostrils
  - Rarely swallowed
    - Traffickers, eluding capture
    - Massive amounts are absorbed through GI tract
  - Effects may be enhanced and confounded by mixing it with alcohol and illicit drugs.

Cocaine

- Metabolism
  - Plasma and liver cholinesterases
  - Half life of 30 minutes to 1 hour
  - Brief, though intense period of intoxication
  - Urine drug screen may detect for about 2 days

Cocaine

- Clinical Effects
  - Euphoria
  - Powerful (sexual, physical, mental)
  - Fully alert – hypervigilant
  - Sympathomimetic effects
    - Pupillary dilation
    - Hypertension
    - Tachycardia
  - Reduced sleep (decreased REM)

Cocaine

- Overdose and Abuse
  - Agitated, irrational, and paranoid
  - Delusions and Hallucinations
  - Sympathomimetic and Dopaminergic effects producing permanent neurologic damage
    - Strokes
      - Within 2 hours of use
      - Most secondary to cranial bleed or ruptured aneurysm
    - Seizures
      - Within 2 hours of use
      - Can occur with first use
      - Often fatal
      - Generalized
      - If begin as partial then generalize, most likely due to stroke
      - Contrast from ETOH and benzos
    - Other Neurologic Complications
      - Involuntary movement disorders (tics), chorea, tremor, dystonia (increased dopamine activity)

Cocaine

- Overdose and Abuse
  - Cognitive Impairment
    - Frequency, nature, and severity are not established
    - No association with chronic dementia
  - Sympathomimetic Effects
    - Tachycardia, Cardiac Arrhythmias, Hypertension
    - Dilated Pupils
    - Myocardial Infarction
    - Stroke

Cocaine

- Treatment of Intoxication and Overdose
  - Respond to seclusion and passage of time
  - Benzodiazepines
    - Suppress agitation
  - Psychosis
    - Will respond to dopamine blocking agents
    - Agents lower the seizure threshold (judicious use)
  - Hypertension
    - May require aggressive treatment
    - Alpha blockers, such as phentolamine, are treatment of choice

Cocaine

- Withdrawal
  - "Crash"
    - Sudden loss of energy
    - Inability to appreciate pleasurable activities
    - Dysphoric Mood
  - Significant cravings
  - Sleep Disturbances
    - Vivid, disturbing dreams (REM rebound)
  - Dopamine agonists and dopamine enhancing medications alleviate some symptoms

Question

A speedball is defined as:

a. a mixture of marijuana and cocaine
b. a mixture of heroin and cocaine
c. simultaneous use of heroin intranasally and intravenously
d. methamphetamine used intravenously
e. heroin used intrathecally

B

Amphetamine

- Types – dextroamphetamine (dexedrine), methamphetamine, methylphenidate (Ritalin)
- Has many medical uses – ADHD
  - Use is paradoxical
  - Stimulate inhibitory neurons

Amphetamine

- Pharmacology
  - Sympathomimetic
  - Similar to cocaine
  - Block dopamine reuptake and stimulate presynaptic dopamine release
  - Usually taken orally, sometimes intravenously
  - Half life is approximately 8 hours

Amphetamine

- Clinical Effects
  - Produce cocaine like effects
    - Hyperalert states
    - Decrease total sleep time and suppress REM
  - Amphetamines last longer
  - May produce a more severe sympathomimetic discharge

Amphetamine

- Overdose
  - Strokes and Dyskinesia (Cocaine like)
    - Hypertension
    - Amphetamine induced vasculitis
  - Seizures rare
  - Thought disorders and hallucinations
  - Chronic use may lead to cognitive impairment, but no evidence for chronic dementia.
  - Treatment is achieved with dopamine blocking neuroloeptics

Question

Chronic abuse of which of the follwing drugs can cause intracerebral vasculitis or hemorrhage, or subarachnoid hemorrhage:

a. Heroin
b. Marijuana
c. d-Amphetamine
d. Phencyclidine
e. Lysergic acid diethylamide

C

Opioids

- Broad term including
  - Medicinal narcotics
  - “Street” narcotics
  - Analgesic neurotransmitters synthesized in CNS
  - Examples: morphine, methadone, heroin, endorphins

Opioids

- Pharmacology
  - Primary action
    - Effect several opioid receptors
      - Delta, Kappa, Mu
      - Located in brain and spinal cord
      - G protein linked and affect adenyl cyclase
  - Also affects dopamine and other neurotransmitters
  - Several antagonists compete with the opioids for the receptor sites
    - Naltrexone (ReVia)
    - Naloxone (Narcan)
  - Duration of effects is normally for several hours

Opioids

- Clinical Effects
  - Therapeutic doses
    - Relieve pain
    - Reduce anxiety
  - Higher doses
    - Lead to a burst of euphoria, a sense of well being, then sleepiness
    - May produce paradoxical agitation, psychosis, and mood changes
  - IV doses routinely lead to nausea and vomitting
    - Direct stimulation of the medulla’s chemoreceptor zone

Opioids

- Overdose
  - Characteristic Triad
    - Coma, Pin-point pupils (miosis), and respiratory depression (decreased rate)
      - Decreased respiratory rate due to effects on CNS respiratory drive center
        - Located adjacent to chemoreceptor trigger zone
      - Leads to cerebal hypoxia with cerebral cortex and basal ganglia damage
  - Rarely leads to seizures
  - Cognitive impairment can result secondary to cerebral hypoxia
    - No correlation with chronic use at appropriate doses

Opioids

- Treatment of Overdose
  - Life threatening aspect is respiratory depression
  - Establish airway and support vital functions
  - Administer narcotic antagonist
    - Naloxone (Narcan)
  - Most patients are comatose and require no further treatment
  - After Narcan, may show signs of withdrawal and require treatment

Opioids

- Withdrawal from Chronic Use
  - Symptoms
    - Intense drug seeking, dysphoric mood, lacrimation, abdominal cramps, piloerection, and autonomic hyperactivity
  - Heroin
    - Withdrawal begins several hours after last dose and peaks at 1-3 days
  - Methadone
    - Withdrawal begins 1-2 days after last dose and peaks at 6 days after last dose
  - Treatment
    - Alpha-2 Norepinephrine agonist alleviates some symptoms

Opioids

- Other Clinical Aspects
  - Health care employees are at particular risk for opioid abuse
    - Demerol and Fentanyl are commonly used
  - Administration of synthetic analogue of meperidine, MPTP, induces parkinsonism
  - Phenytoin enhances methadone metabolism and may precipitate opioid withdrawal
  - Heroin more readily penetrates the blood-brain barrier than morphine

Question

Miosis or pupillary constriction is most often associated with an overdose of which of the following substances

a. LSD
b. Heroin
c. Phencyclidine
d. Cocaine
e. Cannabis

B

Question

Severe opiate overdose is appropriately treated with:

a. naloxone
b. naltrexone
c. pentazocine
d. buprenorphine
e. levo-alpha-acetylmethadol

A

Hallucinogens

- Diverse group of subtances:
  - Lysergic acid diethylamide (LSD)
  - Morning glory seeds
  - Mescaline
  - MDA (old ectasy)
  - MDMA (new ectasy)
- Normally ingested orally
- Rapidly returning to popularity
  - No longer just “rave” drugs

Hallucinogens

- No specific criteria for dependence
- Use is often limited to only a few times a week
- Rapid tolerance to the psychedelic effects, but not to the autonomic effects.
- Cross tolerance between LSD and MDMA
- No evidence of withdrawal but there is still craving

Hallucinogens

- Clinical effects
  - Autonomic
    - Mydriasis
    - Hyperreflexia
    - Hypertension
    - Increased body temperature
    - Piloerection
    - Tachycardia

Hallucinogens

- Clinical Effects
  - Alters Perceptions
    - Intensifies perceptions
    - Derealization
    - Depersonalization
    - Illusions
    - Synesthesia – blending of the senses
    - Hallucinations – normally do no occur at low dose
  - Hallucinations
    - Normal visual only
    - Often of geometric forms and sometimes of persons or places
    - Reality testing usually preserved

Hallucinogens

- Treatment of intoxication
  - Talked down with reality orientation and reassurance
  - Benzodiazepines may provide sedation
- Treatment of overdose
  - MDMA overdose
    - Hyperpyrexia
    - Dehydration
    - Tachycardia
    - Death
  - Treat medically for autonomic symptoms

Hallucinogens

- MDMA Hangover
  - Insomnia, Fatigue, Drowsiness, Jaw Pain
- Hallucinogen Psychotic Disorder
  - May be brief or may lead to a long lasting psychotic episode
- Post Hallucinogen Perception Disorder
  - “flashbacks” – reexperiencing one or more perceptual symptoms while intoxicated
  - Usually fleeting
  - Triggers include stress, drug use, emergence into a dark area, or even by intention
  - Must be distinguished from delusional disorder, migraines, seizures, etc.

Question

The most commonly abused hallucinogens are associated with:

a. physiological dependence

b. hallucinogen withdrawal syndrome

c. tolerance to euphoric effects

d. tolerance to autonomic effects

e. lack of cross-tolerance

C

Question

A 16 year old girl is brought to the emergency department after collapsing on the dance floor at a "rave party." She appears dehydrated, complains of nausea, behaves seductively, and is mildly paranoid. The most likely substance involved is:

a. methylenedioxyamphetamine
b. diacetylmorphine
c. cannabis
d. ketamine
e. cocaine

A

Phencyclidine (PCP)

- Pharmacology
  - Simultaneously central analgesic, depressant, and hallucinogen.
  - Swallowed or smoked with tobacco/marijuana
  - Blocks the reuptake of dopamine, serotonin, and norepinepinephrine.
  - Binds to the NMDA receptor and prevents the inlfux of Ca+.

Phencyclidine (PCP)

- Clinical effects
  - Schizophrenia like symptoms
    - Negative sxs (psychomotor retardation, emotional withdrawal)
    - Positive sxs (delusions, paranoia, and hallucinations)
  - Other hallucinogenics normally produce only positive symptoms

Phencyclidine (PCP)

- Overdose
  - Muscle rigidity
    - May lead to rhabdomyolysis and high fevers
  - Vertical nystagmus
  - “Coma”
    - Blank stare and oblivious to pain
  - Seizures which may progress to status epilepticus
  - Psychotic behavior
    - Progresses to violent behavior
  - Chronic use may produce cognitive impairment with memory impairment and confusion
  - Increased risk for schizophrenia

Phencyclidine (PCP)

- Treatment
  - No medicine acts as a PCP antagonist
  - Requires seclusion and sedation
    - Benzodiazepines
  - Symptomatic Treatment
    - Dantrolene to prevent rhabdomyolysis
    - Benzodiazepines for seizures

Question

A severely agitated, delusional, 21 year old woman is brought to the emergency department after reportedly having taken large doses of LSD at a rock concert. “Talking the patient down” and administration of diazepam have had little effect on the patient. Based on this situation, the psychiatrist should order administration of:

a. phenytoin

b. propranolol

c. phenobarbital

d. carbamazepine

e. chlorpromazine

E

Ketamine

- Frequently used veterinary anesthetic
- Pharmacology
  - Chemical structure similar to PCP
  - Binds to the NMDA receptor
    - Does not block dopamine reuptake
- Clinical Effects
  - PCP like effects
  - Less likely to cause hallucinations, thought disturbances, agitation, or violence

Question

A 38 year old patient is brought to the emergency department after experiencing euphoria and reporting feeling like “flying above the dance floor” at a local club. The patient is now socially withdrawn and exhibits nystagmus. Which of the following would most likely produce this constellation of symptoms.

a. Methcathinone

b. Cocaine

c. Amphetamine

d. Ketamine

e. Alcohol

D

Marijuana

- Pharmacology
  - Cannaboid with several psychoactive ingredients
    - Most potent is Δ9-THC
    - Δ9-THC Receptors located in cerebral cortex, basal ganglia, hippocampus, and cerebellum
  - Usually smoked, sometimes swallowed
  - Effects last 1-3 hours, heavy use may cause changes for 1-2 days

Marijuana

- Clinical Effects
  - Euphoria
  - Pleasantly altered perceptions
  - Slows thinking
  - Impairs judgement
  - Decreases REM sleep

Marijuana

- Overdose
  - Severe anxiety or psychosis
    - Benzodiazepines or antipsychotic agents can control these symptoms
  - Not fatal
  - Rarely cause neurologic complications (stroke or seizure)
  - Some reports have linked to permanent inattention, word fluency problems, and impaired executive functions
  - No links to dementia
    - Cognitive impairment are either transient or mild

Marijuana

- Social Considerations
  - Legalization Attempts
    - Mild anticonvulsant activity
    - Reduces intraocular pressure
    - Suppresses chemotherapy induced vomiting
  - Benefits often overstated
    - D2 Dopamine and 5HT3 serotonin antagonists are more effective against vomitting
    - High doses induce hallucinations
    - Associated with motor vehicle accidents

Question

A 22 year old medical student is extremely anxious and has been unable to sleep for the past 48 hours. The patient is extremely tremulous and has a grand mal seizure during a physical examination. The patient could be experiencing withdrawal from which of the following drugs:

a. Cocaine

b. Diazepam

c. Cannabis

d. Oxycodone

e. Phencyclidine

B

Nicotine

- Pharmacology
  - Affects CNS nicotinic receptors
    - Minority of cortex cholinergic receptors
    - Located in dopamine pathways
      - Provide pleasure and modulate affect
      - Nicotine stimulates release of mesolimbic dopamine
  - Cigarettes are main source
    - Unlike other drugs, pleasurable effect is more subliminal

Nicotine

- Main drive to continue smoking is to avoid withdrawal symptoms
  - Anxiety, restlessness, weight gain, tremulousness, and craving
  - Withdrawal may have temporary cognitive impairment
    - Secondary to anxiety, poor concentration, and preoccupation with lack of cigarettes
- Cessation is aided with nicotine replacement.
  - Buproprion (Wellbutrin, Zyban) increases dopamine concentration in mesolimbic system

Question

Abrupt drug withdrawal is most likely to be life threatening for a person addicted to:

a. heroin
b. cocaine
c. naloxone
d. amobarbital
e. phencyclidine

D

Summary

- Many neurologic aspects of drug abuse can be attributed to specific neurotransmitter abnormalities
- Understanding how the neurophysiology is affected allows you to understand the clinical effects and withdrawal symptoms associated with these drugs

Question #1

- Which is the best treatment for cocaine induced severe hypertension?
  - A. Diuretic
  - B. Calcium Channel Blocker
  - C. ACE Inhibitor
  - D. Phentolamine

Answer

- D. An alpha blocker, such as phentolamine, will be the most rapid and effective antihypertensive therapy.

Question #2

- To which receptor does ketamine and PCP bind?
  - A. Dopamine
  - B. Norepinephrine
  - C. Serotonin
  - D. GABA a
  - E. NMDA

Answer

- E. Ketamine and PCP affect ion channels at the NMDA receptor.

Question #3

- What is the effect of opioids on respiration?
  - A. They reduce the respiratory rate.
  - B. They reduce the depth of respirations.
  - C. They increase the rate but reduce the depth.
  - D. They reduce the depth but increase the rate.

Answer

- A. Opioids reduce the respiratory rate. In severe overdoses, they lead to pulmonary edema.

Question #4

- Which of the following is a common effect of marijuana?
  - A. Fatal reaction to overdose
  - B. Seizures
  - C. Strokes
  - D. Reduced REM sleep

Answer

- D.